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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/533,750	12/05/2005	Yoichi Matsubara	10939/2192	5376

29932 7590 01/10/2007

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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	**PAPER NUMBER**
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,750	MATSUBARA ET AL.	
	Examiner	Art Unit	
	Fereydoun G. Sajjadi	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

Applicant's response of October 23, 2006, to the non-final action dated April 21, 2006 has been entered. No claims have been cancelled. Claims 1 and 4 have been amended, and claims 7-17 are newly added. Claims 1-17 are pending in the application and are under current examination.

New Claim Rejections - 35 USC § 112- New Matter

Applicants' claim amendments have necessitated the following new grounds of rejection.

Claims 10-12 and 16 are newly rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art (hereafter the Artisan), that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

Claims 10 and 16 recite: "hybridization to the target sequence does not substantially occur". The instant specification is devoid of any description for hybridization of the probe not substantially occurring. Applicants state that support for the amendment appears, at least at paragraphs [0047]. However, no specific support for the hybridization of the probe "substantially occurring" is present in the substitute specification.

Claims 11 and 12 recite: wherein the Tm of the hybridization probe is lower than the Tm of "the at least one labeled primer". Applicants state that support for the amendment appears, at least at paragraphs [0048]. However, no specific support for the limitation of "the at least one labeled primer" for hybridization to the probe is apparent from the substitute specification, because the hybridization referred to in paragraph [0048] is in relation to both primers.

Thus, at the time the application was filed, an Artisan of skill would not recognize from the disclosure that Applicant was in possession of either the hybridization probe "substantially occuring", or the "at least one labeled primer", as claimed.

MPEP 2163.06 notes: "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure"

This is a new matter rejection.

Response to Claim Rejections - 35 USC § 112- Second Paragraph

Claims 1-3 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite, in the previous office action of April 21, 2006.

Applicants have traversed the rejection. Applicants' arguments are found persuasive, in view of Applicants' clarification of the language relating to "target base sequence" and the description of "target base sequence" provided in the specification. Thus, the rejection is hereby withdrawn.

New Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Applicant's claim amendments have necessitated the following new grounds of rejection.

Claims 10 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 is unclear in the recitation of "hybridization to the target sequence does not substantially occur", because the use of such relative terminology fails to define how much hybridization is permitted in the reaction. Thus, the metes and bounds of said hybridization remain undefined.

Claim 15 is unclear in the recitation of "at about a middle of the hybridization probe". As the specification fails to limit the number of bases from the middle of a hybridization probe that constitute the "about the middle", the metes and bounds of "about a middle" remain undefined.

Response to Claim Rejections - 35 USC § 103

Claims 1, 3, 4 and 6, were previously rejected under 35 U.S.C. §103(a) as being unpatentable over Lay et al. (Clin. Chem. 43(12):2262-2267; 1997), in view of Klepp et al. (Biochemica 2:14-16; 2000), and claims 2 and 5 were rejected under 35 U.S.C. 103(a) as being unpatentable over Lay et al. in view of Klepp and further in view of Gunneberg et al. (Clin. Chem. 39(10):2157-2162; 1993), in the previous office action dated April 21, 2006.

The amendment of the claims to introduce new claim limitations effectively overcomes the art of record. Thus the rejection of the claims over the cited prior art is hereby withdrawn.

New Claim Rejections - 35 USC § 103 & Response to Arguments

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly

owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Applicant's claim amendments have necessitated the following new grounds of rejection.

Claims 1, 3, 4, 6-12, 14 and 16 are rejected under 35 USC 103(a) as being unpatentable over Link et al. (U.S. Patent No: 5,635,347; Jun 3, 1997), in view of Klepp (Biochemica 2:14-16; 2000) and further in view of Fu et al. (U.S.Patent No: 6,583,112; filed July 17, 2000).

The term kit is not given any patentable weight, as it is directed to a composition.

Link et al. describe a method of detecting a nucleic acid sequence of interest in the amplification product of a PCR reaction, said reaction comprising primers, wherein one primer is labeled with a first label and the PCR reaction is conducted in the presence of an alternately labeled probe (Abstract and Fig. 1). The authors state that the labeled probe is not incorporated into the PCR product and the labels may include biotin or digoxigenin (column 4). In Example III, Link et al. describe the application of their assay to discriminate between genes which had few mutations (including a deletion) compared to the normal cystic fibrosis gene (column 9). Lay et al. do not describe the detection of the hybrid following probe hybridization, by affinity chromatography on a test strip and do not restrict the length for the probe to any particular size.

Klepp describes a DNA detection test strip for the rapid detection of labeled PCR products. Specifically described are 5'-end labeled PCR primers that may be pre-labeled with digoxigenin (first column, p. 14). Klepp additionally states: "In cases where a labeled primer and a labeled oligonucleotide (hybridization probe) are used together in a PCR, verify that the primer and oligonucleotide do not hybridize to each other." (second column, p. 14). Therefore, teaching that the oligonucleotide sequence (hybridization probe) should be designed not to inhibit the DNA amplification (i.e. hybridization to the target base sequence does not substantially occur). Klepp further describe a biotinylated hybridization probe (second column, p. 15) and the details of the chromatographic test strip containing anti-DIG-gold conjugate and streptavidin for detection of the first and second labeling agents (second column, p. 14 and first column, p. 15). Klepp does not teach a hybridization probe with length of 10-15mer.

The use of labeled oligonucleotides in the 10-15 mer range to detect PCR amplification products was well known in the prior art at the time of the instant invention. For example, Fu et

al. describe probes and primers for detecting WRN genes and mutants thereof, wherein the probes are capable of hybridizing under conditions of either high or moderate stringency. The authors state that the cellular nucleic acid is subjected to an amplification procedure, such as PCR and the mutants of WRN may be detected by hybridization with allele-specific oligonucleotide probes, that may be as few as 12 nucleotides in length, usually about 14 to 18 nucleotides in length. They additionally state that the selection of probe size is somewhat dependent upon the use of the probe, and is within the skill of the art (columns 3 and 18). Therefore, as the Tm of the hybridization probe must necessarily be lower than the Tm of at least one labeled primer to prevent interference with the PCR reaction, the degree to which the Tm of the labeled primer would be lower than that of any given primer would depend both on the length and the sequence composition of the probe sequence, both of which are within the control of the design by a person of ordinary skill in the art, as indicated by Fu et al. The mutations detected by Fu et al. are summarized in Table 6 and included deletions and point mutations.

The methods described by both Link et al. and Klepp et al. are directed to the PCR amplification and detection of sequences using differentially labeled primer and hybridization probes, and the methods of Link et al. and Fu et al. are directed to detection of gene mutations, including point mutations. Thus a person of ordinary skill in the art would be motivated to combine the mutation detection method of Link et al. using the short hybridization probes taught by Fu et al., as a matter of design choice, and the test strip affinity chromatographic method of Klepp, to rapidly detect a mutation following amplification and hybridization.

Therefore, it would have been *prima facie* obvious to someone of ordinary skill in the art at the time of the instant invention to utilize the combination of the point mutation detection method of Link et al . and Fu et al., and the test strip affinity chromatographic method of Klepp, resulting in the practice of the instantly claimed invention. A person of ordinary skill in the art, would have been motivated to combine the elements of differentially labeled PCR primer and hybridization probe, together with the detection method utilizing affinity chromatography test strip, and would have a reasonable expectation of success in detecting a mutation site in a sequence, because the PCR mediated amplification of a target sequence and specific detection of a mutation site are enabled by the procedures described by Link et al., Fu et al. and Klepp. Moreover, each

limitation contained in the composition (kit) of claim 4 is effectively described by the teachings of Lay et al., Fu et al. and Klepp.

Claims 1, 2, 5, 15 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Link et al., Klepp and Fu et al. as applied to claims 1, 3, 4, 6-12, 14 and 16 above, and further in view of Gunneberg et al. (Clin. Chem. 39(10):2157-2162; 1993; of record).

Link et al. describe a method of detecting a nucleic acid sequence of interest in the amplification product of a PCR reaction, wherein one primer is labeled with a first label and the PCR reaction is conducted in the presence of an alternately labeled hybridization probe. Klepp describes a DNA detection test strip for the rapid detection of labeled PCR products in a reaction mixture containing 5' digoxigenin -end labeled PCR primers and biotin labeled hybridization probe. Fu et al. describe allele-specific oligonucleotide hybridization probes that may be as few as 12 nucleotides in length for detecting WRN gene mutations, wherein the probes are capable of hybridizing under conditions of either high or moderate stringency.

Link et al., Klepp and Fu et al. do not teach the inclusion of an unlabeled oligonucleotide having a base sequence different in a single base at the position of the point mutation from the base sequence of the labeled hybridization probe, said mutation located at about the middle of the hybridization probe. Gunneberg et al. describe a competitive assay to improve the specificity of detection of single-point mutations (i.e. any type of single point mutation; Title). Specifically described are a normal allele of the α–1 antitrypsin gene, referred to as M, and a single-point mutation referred to as Z, and mixed amplified products containing M and Z alleles of a polymerase chain reaction incubated with a two fold molar excess of unlabeled oligonucleotide, wherein the products were incubated with unlabeled M-specific oligonucleotide, followed by hybridization with radiolabeled Z-specific oligonucleotide, and *vice versa*, in an assay that increased the specificity of single-point mutation detection and improved signal to noise ratio (p. 2161). The sequences of the allele-specific oligonucleotide probes shows the position of the mutation at about the middle of the sequences (p. 2159).

The methods described by Link et al., Fu et al., Klepp and Gunneberg et al. are directed to the PCR amplification and detection of mutations that include single point mutations. Thus, a

person of ordinary skill in the art would have been motivated to combine the differentially labeled point mutation PCR reaction method of Link et al., using short oligonucleotide hybridization probes described by Fu et al. and the test strip affinity chromatographic detection method of Klepp, with the hybridization specificity enhancing method of Gunneberg et al. to reduce false positive signals and detect the point mutation of interest with greater specificity.

Therefore, it would have been *prima facie* obvious to someone of ordinary skill in the art at the time of the instant invention to utilize the combination of the point mutation detection method of Link et al., and Fu et al. together with the point-mutation enhancing method of Gunneberg et al. and the test strip affinity chromatographic method of Klepp, resulting in the practice of the instantly claimed invention. A person of ordinary skill in the art, would have been motivated to combine the elements of differentially labeled PCR primer and hybridization probe, and the hybridization specificity enhancing method together with the detection method utilizing affinity chromatography test strip, and would have a reasonable expectation of success in detecting a point mutation, because the PCR mediated amplification of a target sequence and specific detection of a mutation site are complementary procedures described by Link et al., Fu et al., Gunneberg et al. and Klepp. Moreover, each limitation contained in the instant claims is effectively described by the teachings of Link et al., Fu et al., Gunneberg et al. and Klepp.

Applicants have argued that Klepp does not teach or suggest hybridizing the amplified DNA to a hybridization probe with length of 10-15 mer and teaches away from such feature by requiring that the size of the labeled oligonucleotide hybridization probe must range between 17-40 bases. Applicants' arguments have been fully considered, but are not found persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In an obviousness rejection, Klepp is not required to teach each and every element of claim 1. Regarding the teaching away from a probe length of 10-15 mer, it is noted that Klepp is a publication guideline for a commercial test strip product. As such, the publication specifies optimal conditions for achieving

a signal following hybridization of the probe to the target PCR product. There is no teaching or suggestion by Klepp that a probe length of less than 17 mer would not work. While both the prior art of record and the instant specification note that shorter probe lengths result in poorer signal to noise ratios, the prior art of Fu et al. teaches that hybridization probes as short as 12 mer may be utilized, based on the particular application and design by a person of ordinary skill in the art. Thus, a person of ordinary skill in the art in considering the teachings from the totality of the prior art would not be taught away by the teachings of Klepp.

Applicants have argued that Gunneberg does not teach or suggest all the requirements of claim 2 and requires the sequential hybridization of the unlabeled and labeled probes and teaches away from joint hybridization with a labeled probe and an unlabeled competitive probe by citing previous studies. Such is not persuasive, because as indicated in the preceding, as single reference is not required to teach all the requirements of a claim in an obviousness rejection that is based on a combination of references. Furthermore, Gunneberg et al. in referring to previous studies using competitive assays using labeled and unlabeled oligonucleotides used simultaneously in the hybridization reaction, note the requirement for a 20-fold molar excess of unlabeled allele-specific oligonucleotide. However, this observation would not be considered a teaching away, because it is apparent that simultaneous hybridization remains effective in detecting mutations and reducing signal to noise ratio. Furthermore, a person of ordinary skill in the art would recognize from the teachings of Gunneberg et al. that simultaneous hybridization is an alternative to sequential hybridization and that an additional hybridization step could be avoided by simply increasing the amount of unlabeled allele-specific oligonucleotide in the reaction. Thus, simultaneous hybridization constitutes an effective alternative in mutation detection.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is **(703) 272-3311**. The examiner can normally be reached Monday through Friday, between 7:00-4:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on **(571) 272-0739**. The fax phone number for the organization where this application or proceeding is assigned is **(571) 273-8300**. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Examiner, USPTO, AU 1633

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